·综述·

霍奇金淋巴瘤治疗进展

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Research progress of treatment in Hodgkin lymphoma

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霍奇金淋巴瘤(HL)是一种淋巴系统恶性增殖性肿瘤,我国HL发病率约占所有淋巴瘤的10%,欧美发病率略高。HL好发于15~34岁的年轻人和>50岁的老年人。目前大部分患者接受ABVD方案(多柔比星+博来霉素+长春新碱+氮烯咪胺)作为一线治疗方案疗效较好,治愈率可达80%。但仍有约20%的HL患者难治或复发,成为临床治疗的难点及挑战。近年来随着精确放化疗及靶向药物、免疫治疗等新技术、新药物的应用,HL的治疗取得了快速进展。本文就近年来HL治疗的研究进展进行综述。

一、早期HL一线治疗

由于HL好发于青年且可治愈,放化疗带来的不良反应和继发肿瘤风险很大程度上影响了患者的远期生存质量,因此在保证疗效的基础上减少放化疗疗程和剂量成为早期HL临床研究的重点。近年来提出用更精确、不良反应更低的累及部位放疗(ISRT)取代传统的累及野放疗(IFRT),然而仍无大型随机对照试验证实前者的优势。

1. 预后良好组:对于早期预后良好的HL,2个周期ABVD方案序贯20 Gy IFRT是当前被广泛接受的综合治疗模式(CMT)。德国霍奇金研究组HD7和HD10试验更新数据显示,CMT的15年无进展生存(PFS)显著优于扩大野放射治疗(EFRT),而2个周期ABVD方案序贯20 Gy IFRT组的10年PFS和总生存(OS)与4个周期ABVD方案序贯30 Gy IFRT相比表现出非劣效性[1]。而依据多项大型临床试验结果,中期PET-CT评估阴性未行放疗的疗效仍劣于CMT,主要表现为复发风险增高[2-4]。

2. 预后不良组:对于早期预后不良的HL,HD8及HD11更新数据表明在远期PFS方面,EFRT较IFRT无优势,BEACOPP方案(博来霉素、依托泊苷、多柔比星、环磷酰胺、长春新碱、甲基苄肼、泼尼松)较ABVD方案无优势,4个周期ABVD方案序贯30 Gy IFRT组优于20 Gy组,BEACOPP方案后IFRT高、低剂量组差异无统计学意义[1]。由此提示中等强度的化疗方案或许可以减少放疗剂量。H9-U试验证实4个周期ABVD方案序贯IFRT、4个周期BEACOPP方案序贯IFRT与6个周期ABVD方案序贯IFRT相比均无劣势,但BEACOPP方案的不良反应更多。HD14试验显示,与传统的4个周期ABVD方案联合放疗相比,2个周期BEACOPP增强方案序贯2个周期ABVD方案联合放疗在肿瘤控制方面效果更好[5]。因此4个周期ABVD方案序贯30 Gy IFRT是早期预后不良HL的标准治疗,但对于年龄<60岁耐受性较好患者,中高强度的化疗方案序贯放疗是更优选择。

综上,ABVD方案序贯IFRT/ISRT是早期HL的基本治疗模式,在充分权衡疾病控制和治疗相关不良反应的基础上,可个体化地调整放化疗强度。

二、晚期HL一线治疗

1. 化疗:晚期HL通常采取系统性化疗,放疗仅限于化疗后有残留病灶的患者。ABVD方案仍是目前广泛使用的一线治疗方案,然而国际预后评分(IPS)高危患者的疗效劣于低危患者。一项包括9 993例患者的系统回顾和荟萃分析显示:BEACOPP增强方案的OS在所有化疗方案中显示出明显优势,5年OS率较ABVD方案高10%[6]。HD15试验将2 182例18~60岁晚期HL患者随机分为8个周期、6个周期BEACOPP增强方案和8个周期BEACOPP-14方案三组,中位随访102个月,6个周期BEACOPP增强方案的有效性和安全性最佳。此外根据治疗中期疗效动态调整治疗方案也是近年HL一线治疗的热点。在西南肿瘤协作组的S0816试验中,2个周期ABVD方案后评估PET-CT(PET2)阴性者继续4个周期ABVD方案治疗,PET2阳性者更换为6个周期BEACOPP增强方案治疗[7],更新数据显示患者的5年OS率仍然很高(94%)。尽管历史数据表明PET2阴性者预后良好,但仍有近25%的患者复发,表明PET-CT指导下的ABVD标准一线治疗方案在晚期HL中存在一定局限性。PET2阳性者的PFS优于历史数据,但继发恶性肿瘤的发病

率较高[8]。HD0801试验则提示PET2阳性者受益于包含异环磷酰胺挽救化疗后的自体造血干细胞移植(ASCT)[9]。PET2阴性患者可不应用博来霉素,从而避免肺毒性[10]。

2. Brentuximab vedotin(BV)、nivolumab(nivo)联合AVD方案:BV是一种靶向CD30的抗体耦合药物,选择性地将抗微管蛋白药物MMAE传递给$CD30^+$细胞,从而诱导细胞凋亡。鉴于BV在ASCT失败后HL患者中的高效性,FDA在2011年批准其单药治疗复发难治性HL。ECHELON-1是一项旨在比较BV+AVD方案和ABVD方案作为初治晚期HL患者一线治疗的随机Ⅲ期试验,数据表明BV+AVD方案的2年PFS率优于ABVD方案,且在亚组分析中,IPS 4~7分的高危患者尤其受益于BV+AVD方案[11]。2018年3月,FDA批准BV+AVD方案作为Ⅲ、Ⅳ期HL的一线治疗方案。此外,比较BrECADD方案(BV、依托泊苷、环磷酰胺、多柔比星、达卡巴嗪和地塞米松)和BEACOPP增强方案治疗晚期HL的随机Ⅲ期试验正在进行中。Nivo是靶向程序性死亡受体1(PD-1)的免疫检查点抑制剂,CheckMate 205试验中,nivo单药序贯nivo+AVD方案治疗初诊晚期HL的完全缓解(CR)率为67%,9个月的PFS率为94%,3~4级不良事件的发生率为59%,包括中性粒细胞减少(49%)和发热性中性粒细胞减少(10%),未见明显肺毒性[12]。

三、老年HL一线治疗

大约三分之一初诊HL患者年龄≥60岁[13],与年轻患者相比,老年HL诊断时为晚期病变、有B症状以及EB病毒阳性的患者较多[14]。此外,老年患者体能状态差,合并症多见,预后往往较差。加之放化疗相关损伤,此类患者的OS率并不优于一线强化方案。以往纳入临床试验的≥60岁患者仅占5%~10%,因此大部分治疗进展仅限于年轻群体[15]。HD13和HD10试验中,287例早期预后良好老年HL患者分别接受2个周期AVD方案、2个周期ABVD方案和4个周期ABVD方案序贯IFRT治疗,前两组的CR率为96%~99%,3~4级不良事件发生率相当,而4个周期ABVD方案组CR率为88%,原因可能是博来霉素相关不良反应导致更多患者死亡[16]。因此,对于老年HL的一线治疗,超过2个周期的博来霉素不良反应多,疗效有限。目前临床上老年晚期HL尚无标准一线治疗方案。HD9研究表明,对于66~75岁的晚期HL患者,COPP-ABVD交替方案和BEACOPP方案在5年CR、OS和无治疗失败生存率方面差异无统计学意义,即使应用BEACOPP方案,治疗相关死亡率也较高[17]。前文所述的ECHELON-1显示老年患者组的PFS并未从BV+AVD方案中获益,且BV+AVD方案组发热性中性粒细胞减少的发生率(37%)较预期更高[8]。德国科隆大学医学院报告了B-CAP(BV联合环磷酰胺、多柔比星、泼尼松)方案治疗老年晚期HL患者的Ⅱ期临床试验的初步结果,在接受6个周期B-CAP方案及PET-CT阳性残留灶放疗的48例患者中,21例获得CR,26例获得部分缓解(PR),客观缓解率(ORR)为98%。所有CR患者、10例PR患者PET-CT阴性,2例患者由于不良反应分别在4个周期和5个周期后停止治疗[18]。基于R-CHOP方案衍生的B-CAP方案在老年晚期HL中表现出了良好的有效性和安全性,值得进一步研究。

四、复发难治性HL

1. 挽救化疗:高剂量化疗(HDCT)后ASCT是目前复发难治性HL(RR-HL)患者的标准挽救治疗。而HSCT前的挽救化疗可以减轻肿瘤负荷,且挽救化疗的疗效是ASCT预后评价指标之一。然而,由于缺乏前瞻性随机试验,目前尚无挽救化疗方案的选择推荐。BV单药及BV联合各种传统化疗方案[ICE方案(异环磷酰胺+顺铂+依托泊苷)、DHAP方案(顺铂+阿糖胞苷+地塞米松)、ESHAP方案(依托泊苷+顺铂+阿糖胞苷+甲泼尼龙琥珀酸钠)、苯达莫司汀]作为挽救治疗均显示了良好前景[19-22]。Moskowitz[23]推荐挽救治疗首选BV单药,2个周期后根据PET-CT评估结果再决定是否加用挽救化疗,由此可使一部分患者避免以铂类药物为基础的化疗带来的不良反应,还可筛选出对BV敏感的患者,从而决定ASCT后BV维持治疗的可行性。

2. PD-1抑制剂:PD-1抑制剂在RR-HL中展示了良好的疗效,尤其是ASCT和BV治疗失败的患者[24]。CheckMate 205试验显示nivo在ASCT治疗失败后HL患者中的ORR为69%,更新数据显示无论是否有BV治疗史,nivo反应率高且持久,后续随访中不断有患者达到CR[25-26]。相似的是,KEYNOTE-087试验中的各组患者无论之前接受何种治疗,是否接受过BV治疗,均对pembrolizumab具有显著的反应率[27]。国内的两个代表性PD-1抑制剂sintilimab和tislelizumab治疗RR-HL的ORR分别为80.4%和85.7%[28-29],数据优于国外同类研究,可能由于国内主要纳入二线化疗失败的患者,而国外主要纳入多线治疗、ASCT及BV治疗失败者,此外tislelizumab的IgG4重链区可能会减少Fcγ受体阳性的巨噬细胞吞噬PD-1阳性T细胞,从而发挥更强的抗肿瘤活性[30]。PD-1抗体治疗RR-HL的显著特点之一是在疾病进展后治疗(TBP)中的临床疗效。CheckMate 205中,首次疾病进展至下次系统治疗的中位时间为TBP后8.8个月,而未接受TBP者为1.5个月[26]。鉴于长期使用nivo可持续降低靶病灶的肿瘤负荷,且依然维持较好的耐受性和安全性,患者可在疾病进展后持续使用PD-1抑制剂,除非疾病进展。此外,nivo+BV作为挽救治疗方案的初步数据鼓舞人心[31],但仍需远期随访数据证实其有效性。PD-1抑制剂联合ICE方案作为挽救治疗以及PD-1抑制剂作为ASCT后巩固/维持治疗的多项临床试验正在进行中。

然而,在PD-1抑制剂治疗有效的患者中,仅12%~30%获得CR,且部分患者最终仍复发,中位PFS时间约为14.7个月[26]和10个月[32]。在联合治疗中,CTLA-4单抗Ipilimumab、nivo联合BV治疗22例RR-HL的ORR为82%,CR率为68%;其中既往接受多线治疗,包括ASCT患者的ORR为95%,CR率为79%[33]。目前比较BV+nivo双药和BV+Ipilimumab+nivo三药疗效的随机Ⅱ期试验正在进行中。此外,对于PD-1抑制剂单药治疗无反应的RR-HL患者,LYSA中心研究了化疗及化疗联合免疫治疗的疗效,结

果表明67%的患者对治疗有反应，其中化疗联合PD-1抑制剂治疗组的反应率高于单用化疗组（86%对59%）[34]，这一结论支持化疗与免疫治疗有协同作用。PD-1抑制剂联合其他药物如LAG3抑制剂、PI3K抑制剂、组蛋白去乙酰化酶抑制剂等治疗RR-HL的研究正在进行中。

3. 新型治疗：Chen等[35]提出BV耐药与MMAE抵抗及多药耐药泵表达相关，而环孢素（CsA）能够恢复BV耐药细胞内MMAE浓度，在小鼠模型中联用CsA与BV可恢复BV的敏感性。2018年美国血液学年会报道，将CsA与BV联合治疗原发性BV难治性HL患者的ORR为67%，CR率为33%[36]。此外，标准预处理（FC方案）后进行抗CD30嵌合抗原受体T（CAR-T）细胞治疗对RR-HL具有显著的疗效和安全性[37-38]。新一代口服选择性PI3Kδ/γ抑制剂Tenalisib对复发/难治淋巴瘤有高度活性，在RR-HL中的疗效也引人瞩目[39]。

五、总结与展望

早期HL仍以综合治疗为主，在权衡疗效和不良反应的基础上，可个体化调整放化疗强度。PET-CT指导的治疗为晚期HL患者提供了更精准的方案，BV、nivo联合AVD方案可能成为一线治疗的新选择，而高效、不良反应低的B-CAP方案为老年晚期HL患者提供了新方向。ASCT、PD-1抑制剂、抗CD30-CAR-T及新型药物的合理使用为RR-HL患者带来了希望。

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